REMARKS

In the claims:

Claim 1 is amended to recite "selecting a set of best conformations by lowest energy from the binding conformations for the one or more ligands." Further, claim 1 is amended to rewrite the phrase "to further optimize a subset of the best conformations" as the phrase "further optimizing a subset of the best conformations." Corresponding amendments are made to claims 31 and 48.

Claim 46 is amended to delete the text "ligands; ;" which was inadvertently omitted from the amendments in Applicants' previous reply.

Consistent with claims 1 and 31, claim 48 is amended to delete the inadvertently included phrase "using molecular mechanics."

New claim 56, which depends from claim 48, relates to the subject matter of claim 6.

The preceding amendments are made to make the claims more consistent and definite, and are not intended to limit the claims in any way. Further, no new matter is added. The Examiner is respectfully requested to enter the preceding amendments.

Applicants' Statement of the Substance of the Interview of June 19, 2007

Applicants thank the Examiner for arranging an interview by telephone between Applicants' representatives and the Examiner and his supervising Examiner on June 19, 2007. During the interview, the amendments and arguments herein addressing the rejections of record under 35 U.S.C. § 112, 2nd paragraph were viewed favorably by the Examiners. Moreover, the amendments herein to recite, for example in claim 1, "further optimizing a subset of the best conformations by using annealing molecular dynamics including solvation effects" were suggested by the Examiners to distinguish the amended phrase from the Monte Carlo method in DeWitte.

Claims withdrawn from consideration as directed to a non-elected invention

The Examiner states that claims 48, 49, 52 and 55 are withdrawn as allegedly being independent or distinct from the invention originally claimed. The Examiner alleges that the system could be used in any number of materially different processes, such as automated

sequence alignment. Further, the Examiner states that since Applicants received an action on the merits for the originally presented invention, the original invention is constructively elected for prosecution.

Applicants respectfully traverse the Examiner's restriction. Independent claim 48 is directed to a system for identifying one or more ligand conformations that bind to a protein, the system comprising: a memory; and a processor, wherein the processor is configured to execute instructions operable to conduct the claimed steps, which steps are **identical** to the steps of computer program product claim 31, and, but for verb tense, are identical to the steps of claim 1. Moreover, because the system of claim 48 is configured to execute instructions operable to conduct the steps of claim 31, and the system includes a memory and a processor, claim 48 could be a dependent claim of computer program product claim 31.

Furthermore, the restriction should be withdrawn because there is no serious burden imposed on the Examiner. According to M.P.E.P. § 803, "[i]f the search and examination of all the claims in an application can be made without serious burden, the examiner must examine them on the merits, even though they include claims to independent or distinct inventions." Because the subject matter of the steps conducted by the system of independent claim 48 are identical to the subject matter of the steps of method claim 1 and computer program product claim 31, the Examiner's search for any art relevant to the claims 1 and 31 was automatically a search for any art relevant to the system of claim 48. Therefore, there is no additional burden imposed on the Examiner, let alone a serious burden.

For at least the preceding reasons, the restriction and withdrawal of claims 48, 49, 52 and 55 is improper. Applicants respectfully request that the restriction be withdrawn and claims 48, 49, 52 and 55 be rejoined and examined with the other claims.

If the Restriction is Made Final, the Groups Should be Patentable Over Each Other

35 U.S.C. §121 reads, "If two or more independent and distinct inventions are claimed in one application, the Director may require the application to be restricted to one of the inventions." Thus, restriction is proper only if the inventions are "independent and distinct." M.P.E.P. §802.01 recites (emphasis in original):

> Related [(*i.e.*, not independent)] inventions are distinct if the inventions as claimed are not connected in at least one of design, operation, or effect (*e.g.*, can be made by, or used in, a materially different process) and wherein at least one invention is PATENTABLE (novel and nonobvious) OVER THE OTHER (though they may each be unpatentable over the prior art).

Applicants assert that the pending claims do not recite independent inventions, but that one or more claims may represent related inventions. Consequently, should the requirement for restriction in the instant application be made final, the Examiner is respectfully requested to rule, where applicable, that the claims under examination in the Office Action mailed January 24, 2007 and withdrawn claims 48, 49, 52 and 55 "ARE PATENTABLE (novel and unobvious) OVER EACH OTHER."

Rejections under 35 U.S.C. § 112, 2nd Paragraph

Claims 1, 2, 4, 6, 9-14, 16, 31, 36-42, 45, 46, 47, 50, 51, 53 and 54 stand rejected under 35 U.S.C. § 112, 2nd paragraph, as allegedly being indefinite.

The Examiner alleges that the term "best conformations" is indefinite, and requests clarification. In the telephone interview conducted June 19, 2007, it was agreed that amending the first recitation of "best conformations" to recite "a set of best conformations by lowest energy" would address the rejection. Since the independent claims have been amended accordingly, the rejection is overcome. Applicants respectfully request that it be withdrawn.

The Examiner alleges that the phrase "using annealing molecular dynamics including solvation effects to further optimize a subset of the best conformations" is unclear. The Examiner alleges that it is unclear in which way "annealing molecular dynamics" includes solvation effects, and further alleges that molecular dynamics models and solvation models are known in the art as distinct techniques for optimization. Applicants have clarified the phrase to recite "further optimizing a subset of the best conformations by using annealing molecular dynamics including solvation effects." Moreover, Applicants respectfully note that the specification explicitly describes the use of annealing molecular dynamics in combination with solvation effects, for example in paragraph [0040]:

> Annealing molecular dynamics was performed on a subset of the energy minimized ligand conformations (e.g., from about 1% to about 20% or more of these configurations)

> using MPSim software, K. -T. Lim, et al. (1997) J. Comput. Chem. 18, 501-521, which is incorporated by reference herein, using a full atom force field and solvation effects, such as a continuum description of the solvation using Poisson-Boltzmann method (PBF), D. J. Tannor, et al. (1994) J. Am. Chem. Soc. 116, 11875-11882, or the surface generalized Born (SGB) model, A. Ghosh, et al. (1999) J. Phys. Chem. B. 102, 10983-10990, both of which are incorporated by reference herein. . . . Annealing molecular dynamics simulations were performed in 5 to 10 cycles of 1 ps at each temperature from 50K and 600K in steps of 20K, using the DREIDING force field, a nondistance-dependent dielectric constant of one, and a nonbond list cutoff of 9 Å. Those skilled in the art will recognize that other known atomic forcefields, including, for example, the AMBER, CHARMM, or MMFF forcefields can be used in the MD simulations in place of the DREIDING forcefield described here.

In the telephone interview conducted June 19, 2007, Applicants' representatives discussed the clarifying amendment and pointed out the above support in the specification. Accordingly, because the step of further optimizing a subset of the best conformations by using annealing molecular dynamics including solvation effects is clear and definite, Applicants request that the corresponding rejection be withdrawn.

The Examiner alleges that the metes and bounds of the phrase "optimizing the best conformations using molecular mechanics" is unclear because the specification does not define or fully and completely describe "molecular mechanics." In the telephone interview conducted June 19, 2007, Applicants' representatives pointed out that "molecular mechanics" is a term of art that is understood by one of ordinary skill, who would understand "molecular mechanics" in this context to mean methods of using molecular mechanical force fields in the energy minimization of the ground state of molecules, e.g., the ligand-protein conformations regarded by the claimed invention. Accordingly, because the term "molecular mechanics" is a term of art that is clear and definite to one of ordinary skill in the art, Applicants request that the corresponding rejection be withdrawn.

Rejections under 35 U.S.C. § 102

Claims 1, 2, 4, 9, 11, 12, 16, 29, 31, 36, 37, 39, 40, 46, 47, 50, 51, 53 and 54 stand rejected under 35 U.S.C. § 102, as allegedly being anticipated by DeWitte and Shakhnovich, *J. Am. Chem. Soc.*, 1996, volume 118, pages 11733-11744 ("DeWitte", hereinafter).

However, DeWitte does not anticipate the claimed invention because DeWitte neither describes each and every element as set forth in the claim nor does DeWitte show the identical invention in as complete detail as is claimed. In particular, DeWitte does not disclose the same number of steps or the same steps as claimed.

The law requires that "a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Moreover, "[t]he identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). Thus, a reference that fails to describe even one of the elements as set forth in the claim does not anticipate the claim.

The claimed invention is (claim 1) directed to a method of identifying one or more ligand conformations that bind to a protein, wherein the method is performed by a programmable processor executing a program of instructions, the method comprising the steps in the left column of the following table. For comparison, the Examiner's alleged equivalent steps from DeWitte are shown in the right column. This table is presented only to enable the following arguments by organizing the alleged steps in relation to the claimed steps; Applicants expressly do not concede anticipation of any claimed step by any alleged equivalent step from DeWitte, either in the table or in the following arguments. Further, when quoting the Office Action, comments or insertions by Applicants are shown in {} brackets to avoid confusion with the [] brackets used in the Office Action.

Claim 1	**Examiner's alleged equivalent step from the DeWitte reference**
obtaining structural information for the protein and for one or more ligands;	
identifying at least one binding region of the protein;	
applying a coarse-grained docking algorithm to identify a plurality of binding conformations for the one or more ligands in the binding region;	"a coarse grained docking algorithm (i.e. Monte Carlo growth algorithm) to identify a plurality of binding conformations with low energy configurations [p11735, Col. 1 ¶2]" (Office Action, p 5, lines 19-21)
selecting best conformations from the binding conformations for the one or more ligands;	
optimizing the best conformations using molecular mechanics;	"DeWitte et al. indeed teach the use of CHARMM for minimization (i.e. optimization of interaction energies of designed ligands [Fig. 5] and [p. 11737, Col 2, ¶1] . . . Therefore, the Examiner maintains that DeWitte et al. indeed teach optimizing a selection of best configurations using molecular mechanics, as in amended claim 1" (Office Action, p 5, lines 4-8)
further optimizing a subset of the best conformations by using annealing molecular dynamics including solvation effects;	"DeWitte et al teach a course{*sic*}-grained docking algorithm (i.e. Monte Carlo growth algorithm) to identify a plurality of biniding conformations with low energy configurations [p. 11735, Col 1, ¶2] that includes solvation effects for scoring (i.e. optimization) [p. 11735, Col. 2, ¶ 4] . . . Furthermore, said algorithm includes temperature control variables [p. 11736, Col. 1, ¶ 7 and Col. 2, ¶ 1]. Therefore, the Examiner has broadly interpreted this as an implicit teaching gor "using annealing molecular dynamics including solvation effects" for further optimization of designed ligands, as in amended claim 1. (Office Action, p 5, 11-19)
minimizing a preferred set of conformations from the subset of the best conformations;	"DeWitte et al teach minimization of a "preferred set of conformations" from the subset of best design ligands and best CHARMM ligands [Figure 5] as in amended claim 1" (Office Action, p 5, lines 19-21)

Claim 1 (continued)	**Examiner's alleged equivalent step from the DeWitte reference (continued)**
calculating a binding energy for each conformation of the preferred set of conformations;	
ranking the conformations of the preferred set of conformations based on the calculated binding energies;	
selecting for each of the one or more ligands the conformation of the preferred set of conformations having the lowest calculated binding energy; and	
outputting a data file comprising a list of selected ligand-protein conformations having the lowest calculated binding energy, and their respective binding energies;	"the SMOG program outputs selected conformations [Table 3] as in amended claim 1" (Office Action, p 5, lines 21-22

DeWitte does not anticipate the claimed invention because DeWitte does not teach the claimed number of steps. For example, claim 1 requires a step of optimizing the best conformations using molecular mechanics **and** a step of minimizing a preferred set of conformations from the subset of the best conformations. The Examiner alleges that both of these steps are anticipated by DeWitte's teaching of the use of CHARMM. However, DeWitte does not teach the use of CHARMM as two distinct, separate steps, let alone a step of optimizing the best conformations using molecular mechanics and a step of minimizing a preferred set of conformations from the subset of the best conformations as claimed. Consequently, the claimed invention is not anticipated by DeWitte because DeWitte does not teach the claimed number of steps.

Moreover, DeWitte does not anticipate the claimed invention because DeWitte does not teach the same steps as the claimed invention. For example, the Examiner alleges that the claimed "annealing molecular dynamics" step is anticipated by DeWitte's "Monte Carlo growth algorithm." As detailed in Applicants' previous reply and explained by Applicants' representatives in the telephone interview conducted June 19, 2007, the Metropolis Monte Carlo criterion taught by DeWitte is a method of selecting between two different branches of

DeWitte's Small Molecule Growth algorithm by comparing two predetermined, static configurations of two **different** molecules. In DeWitte, these two different molecules, the lowest energy rotamer of the present growth step and the lowest energy rotamer of the previous growth step, are different molecules from one another because of the molecular fragment added in the growth step. Moreover, the conformations of these different molecules are static, being determined in the preceding step of fragment rotation and lowest energy rotamer selection, and are not optimized by the Metropolis Monte Carlo acceptance criterion. Thus, the Monte Carlo method of DeWitte involves no optimization of conformations of a particular ligand. In the interview, Examiner Borin suggested that the rejection could be overcome by amending the claimed "annealing molecular dynamics" as an active optimizing step. Accordingly, although Applicants believe that the "annealing molecular dynamics" step as claimed prior to amendment was clearly distinguished from DeWitte, Applicants have amended claim 1 to recite "further optimizing a subset of the best conformations by using annealing molecular dynamics including solvation effects clearly distinguished the claimed invention." Consequently, DeWitte does not anticipate the claimed invention because DeWitte does not teach the same steps.

In conclusion, because DeWitte does not disclose the same number of steps or the same steps as claimed, DeWitte does not describe each and every element as set forth in the claim nor does DeWitte show the identical invention in as complete detail as is claimed. Consequently, DeWitte does not anticipate the claimed invention. Applicants respectfully request that the corresponding rejection be withdrawn.

Rejection under 35 U.S.C. § 103 (a)

Claims 1, 2, 4, 9, 11, 12, 16, 29, 31, 36-40, and 43-45 stand rejected under 35 U.S.C. § 103 (a) as allegedly being unpatentable over Zou, X., *et al.*, *J. Am. Chem. Soc.* (1999) volume 121, pages 8033-8043 ("Zou ") further in view of DeWitte.

The claimed invention is not obvious over Zou, further in view of DeWitte, because these documents do not teach or suggest all of the claim limitations. To establish a prima facie case of obviousness, all of the claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974).

As discussed hereinabove, because DeWitte does not disclose the same number of steps or the same steps as claimed, DeWitte does not describe each and every element as set forth in the claim. These deficiencies of DeWitte are not provided by Zou. In particular, contrary to the Examiner's allegation that Zou provides an implicit teaching for annealing molecular dynamics, Zou does not teach or suggest the use of annealing molecular dynamics. The Examiner alleges that because Zou teaches a generalized Born surface area model and Applicants' priority document discloses that annealing molecular dynamics can be practiced using a generalized Born model, Zou must implicitly teach annealing molecular dynamics.

First, as explained in Applicants' reply filed December 28, 2006, a solvation model for description of free energy estimations **is not equivalent** to an annealing molecular dynamics calculation. Zou describes the use of the Generalized-Born (GB/SA) model of solvation to estimate ligand binding energies, through modifications of the model to account for electrostatic interactions between the ligand and the solvent, and introduces a formula to estimate the binding free energy by calculating a free energy score. Zou is silent regarding annealing molecular dynamics. Consequently, Zou does not teach or suggest annealing molecular dynamics.

Second, by alleging that annealing molecular dynamics can be practiced using a generalized Born model according to Applicants' priority document, the Examiner appears to misinterpret the relation between Applicants' use of annealing molecular dynamics calculations and solvation models. Applicants use solvation models such as the surface generalized Born (SGB) model so that "[a]nnealing molecular dynamics [can be] performed . . . using . . . solvation effects" (specification, [0040]). However, the use of a solvation model in the art does not imply annealing molecular dynamics. Annealing molecular dynamics could be performed without any solvation model at all, for example, for calculations regarding the gas phase, vacuum, or the solid phase. Consequently, Zou 's disclosure of the generalized Born model does not teach or suggest annealing molecular dynamics.

Furthermore, Zou does not teach or suggest the number of claimed steps, either alone or in combination with DeWitte.

For at least these reasons, the claimed invention is not obvious over Zou in view of DeWitte, and Applicants respectfully request withdrawal of the corresponding rejection.

CONCLUSION

For the reasons set forth above, Applicants submit that the claims of the instant application, as amended herein, are in condition for allowance. Reconsideration and withdrawal of the Examiner's objections and rejections are hereby requested. Allowance of the claims is earnestly solicited.

In the event that a telephone conversation could expedite the prosecution of this application, the Examiner is requested to call the undersigned at (650) 839-5005.

Please apply any required charges or credits to deposit account 06-1050.

Respectfully submitted,

Date: June 25, 2007

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